ATS Core Curriculum 2017: Part III. Adult Critical Care Medicine

Series Editor: Jason T. Poston
Part III Editors: Jakob I. McSparron, Margaret M. Hayes, and Andrew M. Luks

Jakob I. McSparron[1], Margaret M. Hayes[2], Jason T. Poston[3], Luke A. Seaburg[4], Amy E. Morris[4], Maryellen Antkowiak[5], Joshua Farkas[5], Janhavi Athale[6], R. Scott Stephens[7], Kenneth W. Dodd[8,9], Matthew E. Prekker[8,9], Peter Hountras[10], Michael J. Cuttica[10], Morgan Soffler[2,11], Kathryn A. Hibbert[11], Timothy Leclair[5], Ryan Clouser[5], and Andrew M. Luks[4]

[1]Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan; [2]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [3]Section of Pulmonary and Critical Care Medicine, Department of Medicine, University of Chicago, Chicago, Illinois; [4]Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; [5]Division of Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Burlington, Vermont; [6]Division of Oncology and [7]Division of Pulmonary and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, Maryland; [8]Department of Emergency Medicine and [9]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota; [10]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [11]Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

ORCID ID: 0000-0002-8356-499X (M.S.).

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The American Thoracic Society (ATS) Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, medical critical care, and sleep medicine, in a 3- or 4-year recurring cycle of topics. The 2017 course was presented in May during the annual International Conference and is published in four parts. This year, Part III covers topics in adult critical care medicine. A Continuing Medical Education (CME) exercise covering the contents of the Core Curriculum can be accessed online at www.thoracic.org until August 2020.

Acute Liver Failure

Luke A. Seaburg and Amy E. Morris

Definition and Disease Scope

Acute liver failure (ALF) is defined as hepatic injury with encephalopathy and coagulopathy (international normalized ratio > 1.5) within 26 weeks of initial hepatic insult (1).

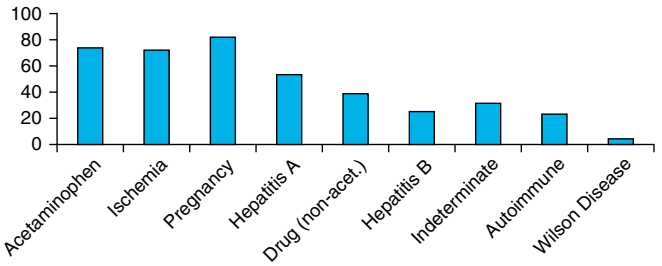

Figure 1. Transplant-free survival by etiology for common causes of acute liver failure, from 1,081 patients in a prospective observational cohort study from 31 liver disease and transplant centers, 2006 to 2013 (3). The *y-axis* shows survival as a percentage. non-acet. = non-acetaminophen.

Acetaminophen toxicity accounts for 46% of all cases in the United States; other medications (e.g., isoniazid, phenytoin) or herbal supplements (e.g., kava, ephedra) account for roughly 12% of cases, and 13% of cases are idiopathic (2). Transplant-free

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Correspondence and requests for reprints should be addressed to Jakob I. McSparron, M.D., University of Michigan, 1500 East Medical Center Drive, TC 3916, Ann Arbor, MI 48109. Email: jmcsparr@med.umich.edu

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Table 1. Hepatic encephalopathy grading scale

Encephalopathy Grade	Manifestation
I	Decreased memory, attention span; often subtle, with only small changes on number connection test
II	Confusion, slurred speech, inappropriate behavior
III	Stuporous, difficult to arouse
IV	Coma

survival rates in ALF have increased over the past 30 years, exceeding 50% in a recent large observational study, but prognosis varies significantly depending on the underlying etiology (Figure 1) (3).

General Treatment Principles

Patients with newly diagnosed ALF should be carefully monitored, ideally in an intensive care unit (1). Diagnostic evaluation should include a review of all prescribed and over-the-counter medications, supplements, herbal remedies, and recreational drugs; laboratory tests, including ceruloplasmin level, autoimmune and viral serologies, and pregnancy test; and hepatic ultrasound with vascular flow assessment. Initial management is focused on monitoring for and treating the common complications of ALF, including hepatic encephalopathy and elevated intracranial pressure (ICP), infection, and coagulopathy.

Hepatic encephalopathy, graded according to the scale in Table 1, is the most common complication of ALF and correlates with degree of liver dysfunction and risk of death. Onset of severe encephalopathy raises the possibility of elevated ICP. Normal ICP is less than 15 mm Hg; a pressure greater than 20 mm Hg is considered intracranial hypertension (ICH), which contributes to a substantial portion of ALF deaths (4).

Assessing ICP is challenging: high admission ammonia level ($>$100 μM) is a risk factor for ICH but does not directly correlate with ICP (5). Invasive ICP monitoring can be initiated in patients with grade III or IV hepatic encephalopathy but should only be performed in experienced centers due to risk of intracranial hemorrhage. Importantly, this intervention has never been shown to improve mortality, with the largest retrospective review to date demonstrating that ICP monitoring changes management but does not improve outcomes (6). Noninvasive ICP monitoring methods lack sufficient evidence to recommend widespread use. Whether measured directly or treated empirically in the setting of severe encephalopathy, ICH can be addressed through several interventions. Table 2 summarizes commonly used therapies discussed in the most recent guidelines from the American Association for the Study of Liver (1).

Prophylactic antibiotics in liver failure are associated with decreased rates of infection; however, despite an increased risk of mortality when infection occurs in the setting of ALF, this intervention has not been associated with mortality benefit (7, 8). Current guidelines instead recommend surveillance cultures and radiographs, with early initiation of antimicrobial therapy when infection is suspected (1).

Due to impaired clotting factor and platelet production, patients with ALF are at risk for hemorrhage. However, because the level of international normalized ratio does not correlate well with the degree of coagulopathy, fresh frozen plasma transfusions should be reserved for procedures or clinically significant bleeding. Prophylaxis with proton pump inhibitors is warranted due to the high risk of gastrointestinal bleeding (1).

Specific Treatment Strategies

N-acetylcysteine (NAC) significantly reduces mortality in acetaminophen overdose and has been shown to increase transplant-free survival in nonacetaminophen ALF, although the mechanism for the latter benefit remains unclear (9). Given the lack of significant side effects, treatment with NAC in ALF of any cause is reasonable until spontaneous recovery or transplant. Other specific therapies are listed in Table 3.

In addition to estimating prognosis on the basis of the underlying etiology of ALF as noted above, the King's College Criteria can be used to predict poor outcomes (death), with a sensitivity and specificity of 69% and 82 to 92%, respectively. All patients with ALF should be screened by these criteria, and those with a high score, or those with rapidly worsening condition, should be considered for urgent referral to a transplant center for further evaluation and management (1). One-year survival rates after transplant are greater than 80% in some centers, but the risks and costs of major surgery, a lifetime of immunosuppression,

Table 2. Interventions for intracranial hypertension

Intervention	Appropriate in Most Cases?	Target	Notes/Caveats
Head-of-bed elevation	Yes	$>$30 degrees	
Vasopressors	Yes	MAP $>$ 75 mm Hg and cerebral perfusion pressure 60–80 mm Hg	If patient not spontaneously meeting targets
Hyperosmolar therapy	Yes	Serum sodium 145–155 mEq/L	In highest-risk patients (severe encephalopathy)
Intravenous mannitol	Yes	Serum osmolality 300–320 mmol/kg	Patient must have intact renal function
Hyperventilation	No	$Pa_{CO_2} < 34$	Acutely reduces ICP but ineffective for prolonged periods; may ultimately impair cerebral perfusion
Therapeutic hypothermia	No	32°–34°C	Some promise in animal studies and small trials; recent randomized trials do not support widespread use (10)

Definition of abbreviations: ICP = intracranial pressure; MAP = mean arterial pressure.

Table 3. Suggested specific therapies for acute liver failure

Etiology	Therapy
Severe alcoholic hepatitis	Corticosteroids improve 28-d mortality, pentoxifylline equivalent to placebo in recent meta-analysis (11)
Autoimmune hepatitis	Corticosteroids
Possible drug hepatotoxicity	Discontinue all supplements, nonessential medications
Hepatitis B	Nucleos(t)ide analog (e.g., lamivudine)
Herpes or varicella zoster infection	Acyclovir
*Wilson disease	Chelation
*Mushroom ingestion	Silibinin or penicillin G (12)

*Highly likely to require transplant.

as well as the need for stable housing, strong social supports, and the abstention from drug and alcohol abuse must be considered.

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Acute Pancreatitis

Maryellen Antkowiak and Joshua Farkas

Background

Acute pancreatitis is among the leading causes of gastrointestinal inpatient admissions in the United States, and severe cases have up to 30% mortality (1, 2). Although patients may develop shock and multiorgan failure, the most common cause of death is delayed or recurrent infections. Meticulous supportive care is the backbone of management.

Diagnostic Strategies

The diagnostic criteria of pancreatitis require two of the following three criteria: abdominal pain, imaging evidence of pancreatitis, and lipase greater than three times the normal limit. All patients should be evaluated with a right upper quadrant ultrasound and liver function tests to rule out gallstones or cholangitis. Computerized tomography scan of the abdomen with contrast is indicated only if the diagnosis is unclear or if the clinical course suggests the presence of complications. Endoscopic retrograde cholangiopancreatography may be indicated if there is evidence of cholestasis or concern for ascending cholangitis.

Resuscitation

Resuscitation guidelines for pancreatitis have evolved similarly to those for sepsis. Although large-volume resuscitation (e.g., fluid boluses followed by 250–500 ml/h, resulting in ~8–14 L of fluid over the first day) was previously widely recommended, the available evidence supports a different approach. Two randomized controlled trials found that greater fluid administration was associated with increasing rates of infectious complications and significantly higher hospital mortality rates than more controlled fluid administration (3, 4).

Given these data, a more suitable approach is to resuscitate patients with pancreatitis as you would patients with sepsis, using a moderate amount of fluid, with vasopressors as necessary to maintain blood pressure. Recent guidelines recommend administering 2.5 to 4 L of fluid over the first 24 hours, consistent with modern sepsis care (2). On the basis of a randomized controlled trial demonstrating lactated Ringer solution was associated with less systemic inflammatory response syndrome and lower levels of C-reactive protein than normal saline, lactated Ringer solution is the preferred resuscitation fluid (5, 6).

Nutritional Support

Traditionally, enteral feeding in pancreatitis was believed to stimulate pancreatic enzyme secretion and exacerbate pancreatic inflammation. However, randomized controlled trials have shown that early enteral nutrition reduces pancreatic infection and mortality and, as a result, enteral nutrition is now recommended once the initial resuscitation phase has concluded (7).

The benefits of enteral nutrition, including prevention of ileus, intestinal atrophy, and bacterial translocation, may be seen even

with slow rates of enteral feeding. Current guidelines suggest starting trophic feeds at a rate of 10 to 20 ml/h and advancing as tolerated, with the goal of providing adequate protein intake as soon as possible (1.5 g/kg daily).

Randomized controlled trials reveal no differences in outcomes between gastric or postpyloric feeding (8). Gastric feeding is typically the initial approach due to the ease of obtaining gastric access, but in patients with poor gastric motility or vomiting, post-pyloric delivery may be preferable.

Nonintubated patients should be fed orally with a low-fat diet as tolerated. If oral feeding is unsuccessful for 3 to 5 days, then placement of a nasoenteral tube is warranted (9).

Antibiotics and Infected Pancreatic Necrosis

Antibiotics should only be given when infection is suspected and should not be used on a prophylactic basis. Diagnosis of infection is challenging, as signs such as fever and leukocytosis can occur in pancreatitis with or without infection. Because bacterial superinfection is rare during the initial phase of pancreatitis, antibiotics can typically be withheld during the initial 7 to 10 days (7).

Initial improvement followed by clinical deterioration may herald an infectious complication. Given that there is no clear evidence regarding whether to initiate empiric antibiotics versus tailoring therapy after percutaneous biopsy of necrotic tissue (7, 10), it is recommended that biopsy decisions be made in consultation with pancreatic surgeons.

Additional Management Considerations

Triglyceride level should be obtained to diagnose hypertriglyceridemia-induced pancreatitis (triglyceride level $>$ 1,000 mg/dl). Patients with this condition may benefit from acute therapies to reduce serum triglyceride levels, including insulin infusion and plasmapheresis, as well as long-term approaches to decrease the risk of recurrent disease.

Abdominal compartment syndrome, defined by elevated bladder pressure ($>$20 cm H_2O) plus organ dysfunction (e.g., acute kidney injury, hypotension, elevated airway pressures), can occur, particularly after large-volume fluid resuscitation. Treatments include paralysis, therapeutic paracentesis, evacuation of bowel contents, and decompressive laparotomy (11).

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Hematologic and Oncologic Emergencies

Janhavi Athale and R. Scott Stephens

Background

Hematology and oncology patients account for up to 30% of all intensive care unit (ICU) admissions. Although many problems (e.g., respiratory failure, shock) are similar to those seen in the general ICU population, there are several unique emergencies that can occur in this patient group of which the critical care practitioner must be aware: neutropenic fever and sepsis, tumor lysis syndrome, leukostasis, and thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS). The latter is not specific to the hematology–oncology patient population but is considered here as it is a primarily hematologic problem.

Neutropenic Fever

Neutropenic fever is defined as a single temperature greater than 38.3°C or greater than 38.0°C for more than 1 hour with an absolute neutrophil count less than 1,500 cells/μl (although many centers use an absolute neutrophil count threshold $<$ 500 cells/μl) (1). Antibiotics should be administered within 30 minutes of recognition, as delays are associated with increased mortality (2). Early investigation for and treatment of sepsis is warranted. Although gram-negative coverage has traditionally been emphasized, gram-positive organisms are now the most common bacteria recovered from neutropenic patients, and current guidelines now recommend empiric gram-positive and antipseudomonal coverage (1). Additional coverage is indicated in patients with known colonization, risk factors, or prior infections with resistant organisms (1). Carbapenem-resistant Enterobacteriaceae (CRE) infection is associated with a 65% mortality rate in hematologic malignancies, and CRE-targeted therapy is important if CRE infection is suspected (3). Antifungal therapy should be considered in high-risk patients with fevers lasting

more than 4 to 7 days or hemodynamic instability despite broad antibiotic coverage (1). In addition to appropriate early antibiotic choice, aggressive diagnostic workup should be pursued, and consideration should be given to early bronchoscopy with bronchoalveolar lavage in patients with neutropenic fever and pulmonary infiltrates.

Current guidelines recommend against routine use of hematopoietic growth factors in established neutropenic fever due to a lack of mortality benefit and theoretical concern for harm due to an overexuberant inflammatory response (1, 4). Growth factors may be considered for patients at high risk for infectious complications or poor outcomes, including age above 65 years, pneumonia, sepsis, and prolonged neutropenia (4).

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is most commonly seen with initiation of treatment of hematologic malignancies (leukemia, lymphoma) but can be seen in other malignancies with large tumor burden and may also occur in the absence of treatment. Associated with mortality rates higher than 15%, it develops as a consequence of rapid cancer cell death leading to electrolyte and metabolic abnormalities, including hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia, which, in turn, can cause arrhythmias, seizures, and acute kidney injury. TLS is graded according to the Cairo-Bishop classification; grade 2 or higher TLS may require ICU-level care (Table 4) (5).

First-line therapy for prophylaxis and management of TLS is hydration (6). Urinary alkalization is not recommended. Because calcium administration can cause calcium phosphate precipitation, treatment is reserved for symptomatic hypocalcemia. The advent of recombinant urate oxidase (rasburicase), which metabolizes uric acid to allantoin, has markedly changed the prophylaxis and treatment of TLS (6). Rasburicase can cause hypersensitivity reactions and should not be used in patients with glucose-6-phosphate dehydrogenase deficiency due to the risk of oxidative hemolysis. Despite optimum management, dialysis is frequently required in severe TLS.

Leukostasis

Patients with acute leukemia can present with leukostasis, in which a markedly elevated blast cell or white blood cell (WBC) count increases blood viscosity and causes vascular occlusion and decreased end-organ perfusion. Clinical manifestations include altered mental status, hypoxemic respiratory failure, and coronary or mesenteric ischemia. Leukostasis is more common in myeloid leukemia than in lymphoid leukemia and typically occurs with a WBC count greater than 50,000 cells/μl, though it can occur at lower WBC counts (7). Treatment consists of hydration and urgent cytoreduction with chemotherapy alone or chemotherapy plus leukophoresis. Although patients may be severely anemic or hypervolemic, it is essential to neither transfuse blood nor diurese, as either intervention can increase serum viscosity and exacerbate leukostasis (8).

TTP and HUS

TTP and HUS should be considered in patients presenting with a combination of anemia, thrombocytopenia, and acute kidney injury (9). The classic pentad of fever, thrombocytopenia,

Table 4. Cairo-Bishop grading classification of tumor lysis syndrome

LTLS	Grade 0* −	Grade I +	Grade II +	Grade III +	Grade IV +	Grade V +
Creatinine[†,‡]	⩽1.5 × ULN	1.5 × ULN	>1.5–3.0 × ULN	>3.0–6.0 × ULN	>6.0 × ULN	Death[§]
Cardiac arrhythmia[‡]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death[§]
Seizure[‡]	None	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizures of any kind that are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death[§]

Definition of abbreviations: ADL = activities of daily living; CHF = congestive heart failure; CTLS = clinical tumor lysis syndrome; LTLS = laboratory tumor lysis syndrome; ULN = upper limit of normal.

CTLS requires one or more clinical manifestations along with criteria for LTLS. Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade. Reprinted by permission from Reference 5.

*No LTLS.

[†]Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional ULN below age/sex-defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: >1 and <12 yr, both male and female, 61.6 μmol/L; ⩾12 and <16 yr, both male and female, 88 μmol/L; ⩾16 yr, female, 105.6 μmol/L; ⩾16 yr, male, 114.4 μmol/L.

[‡]Not directly or probably attributable to a therapeutic agent (e.g., increase in creatinine after amphotericin administration).

[§]Attributive probably or definitely to CTLS.

microangiopathic hemolytic anemia, elevated creatinine, and neurologic symptoms is not present in all cases. If TTP is suspected, plasma exchange should be urgently initiated, because the results of confirmatory assessment of ADAMTS13 activity may take several days. Plasma exchange is superior to plasma transfusion but requires placement of a large-bore catheter in a thrombocytopenic patient. Except in cases of active bleeding, platelet transfusion should be avoided due to an increased risk of thrombosis and mortality (10).

Unlike TTP, the treatment of HUS is primarily supportive and involves treating the underlying infection. Atypical HUS (aHUS), or complement-mediated HUS, is an increasingly recognized entity and is associated with high rates of mortality and renal failure. aHUS is treated initially with plasma exchange, followed by immunosuppression. Recently, eculizumab, a humanized monoclonal antibody against C5, has been shown to be effective in aHUS, although concerns persist about the high cost and prolonged duration of therapy (9).

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Extracorporeal Membrane Oxygenation

Kenneth.W. Dodd and Matthew E. Prekker

Physiologic Foundations

Extracorporeal membrane oxygenation (ECMO) can be used to support a patient with respiratory or cardiac failure refractory to conventional management until the underlying disease improves or the failing organ is replaced. Deoxygenated venous blood is removed via a large-bore cannula and pumped through a synthetic membrane oxygenator. CO_2 removal is controlled by the flow rate of fresh ("sweep") gas through the oxygenator and facilitated by the relatively high solubility and diffusivity of CO_2. The oxygenated and decarboxylated blood is then returned to the patient through either the venous or arterial system, depending on the overarching goal of EMCO support.

If respiratory support is the goal, the return cannula is placed in a central vein, referred to as venovenous (V-V) ECMO. Although traditionally two separate cannulae were used (e.g., femoral drainage, internal jugular return), use of a bicaval, dual-lumen cannula is becoming more common. These cannulae are placed with imaging guidance in the right internal jugular vein and can drain blood from both vena cavae and direct the return of oxygenated blood to the tricuspid valve, potentially minimizing recirculation and allowing patient mobility. With either cannulation strategy, V-V ECMO is in series with the heart (i.e., ECMO blood flow mixes with the patient's remaining venous return and is circulated by native, intact ventricular function). The primary determinants of systemic oxygen delivery in this system are the ratio of ECMO blood flow relative to the patient's cardiac output and the hemoglobin concentration (1).

Patients who also require circulatory support are placed on venoarterial ECMO, in which oxygenated blood is returned to a large artery analogous to partial cardiopulmonary bypass. The venoarterial circuit functions in parallel to the heart, providing cardiac and respiratory support, whereby retrograde ECMO blood flow mixes with any native cardiac output in the aorta (Figure 2).

ECMO Patient Selection and Complications

Appropriate patient selection is critical for minimizing complications and maximizing benefit. Although the specific criteria for initiating ECMO remain the subject of debate, generally accepted indications and contraindications for ECMO are presented in Table 5. Scoring systems to help predict mortality among adults undergoing ECMO have been proposed (2). Even in experienced ECMO centers, ethical issues arise regarding both initiation and withdrawal of extracorporeal support (3).

Frequent complications during ECMO include hemorrhage, thrombosis, vascular injury from cannulation, or kidney injury; rare but potentially catastrophic complications include pump failure, air embolism, cannula migration, and accidental decannulation.

Extracorporeal Support for Acute Respiratory Failure

According to an international ECMO registry, the survival rate to decannulation in V-V ECMO patients is 66% (4). In the only major recent trial of ECMO in adults, the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial found less death or severe disability at 6 months among patients with acute respiratory distress syndrome referred to a specialized center capable of providing V-V ECMO than patients who received conventional mechanical ventilation without transfer (37 vs. 53%; relative risk, 0.69; $P = 0.03$); 76% of patients referred to the ECMO center actually received ECMO in this study (5). Another large randomized controlled trial comparing V-V ECMO to standard-of-care mechanical ventilation is currently underway (6).

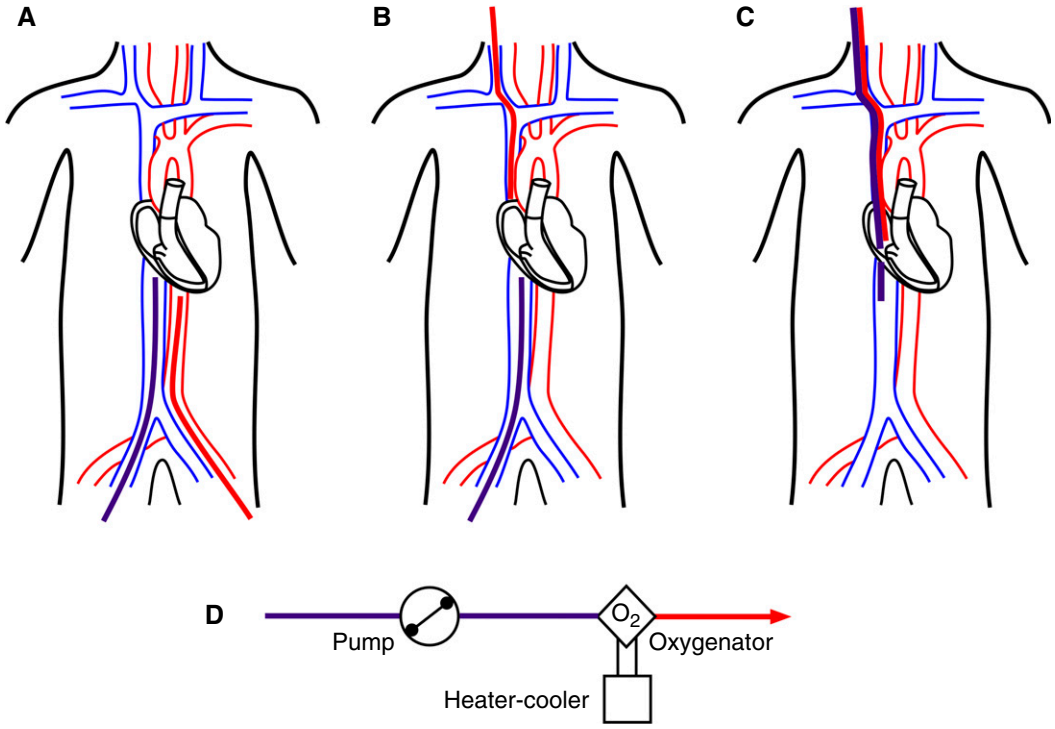

Figure 2. Common cannula placements for venoarterial (V-A) and venovenous (V-V) extracorporeal membrane oxygenation (ECMO) and the common circuitry. In all types of peripheral ECMO, blood is drained from a central vein and pumped through a membrane oxygenator/heater-cooler. (*A*) Oxygenated blood is returned to the arterial system in V-A ECMO, bypassing the heart and lungs. (*B*) Two-site approach to V-V ECMO, whereby oxygenated blood is returned to the superior vena cava via the right internal jugular vein. (*C*) Single-site approach to V-V ECMO using a dual-lumen cannula, whereby one lumen drains blood from the superior and inferior vena cavae and the other lumen returns oxygenated blood to the right atrium, with the return jet ideally directed at the tricuspid valve. (*D*) Common components of an ECMO circuit, with the direction of blood flow indicated by the *arrow*.

Recommendations regarding many key aspects of V-V ECMO care, such as anticoagulation and mechanical ventilation strategies, are largely based on expert opinion, but a research infrastructure is emerging to inform practice (7). Because V-V ECMO efficiently augments gas exchange, an emerging approach is to rest the lungs and prevent further ventilator-induced lung injury by using a pressure-limited, time-cycled mode to limit driving pressure while maintaining positive end-expiratory pressure greater than or equal to 10 cm H_2O (8). Weaning from V-V ECMO generally precedes liberation from mechanical ventilation. Decannulation is considered when gas exchange and lung mechanics are sufficient during a trial of moderate-intensity mechanical ventilation with ECMO sweep gas flow of zero.

There has been recent interest in using low blood flow rates and smaller cannulae to support patients with hypercarbic respiratory failure through extracorporeal CO_2 removal. Technological advances have led to more efficient and compact extracorporeal CO_2 removal systems effectively capable of "respiratory dialysis," although their utility in severe chronic obstructive pulmonary disease exacerbations or acute respiratory distress syndrome complicated by hypercarbia remains under investigation (9, 10).

Access to ECMO

The number of ECMO centers has grown rapidly since the influenza pandemic in 2009–2010 (1). ECMO is resource intensive and requires a multidisciplinary approach, ideally organized within specialized centers capable of providing advanced care for patients with acute respiratory or cardiac failure. A recent position paper advocated a minimum annual ECMO volume of 20 cases (12 cases for respiratory failure specifically) as a benchmark for developing and maintaining expertise, which may require a population catchment area of greater than 2 to 3 million (11).

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Table 5. Commonly used extracorporeal membrane oxygenation indications and contraindications

	V-V ECMO	V-A ECMO
Indications	Absolute inability to maintain adequate oxygenation or CO_2 elimination with mechanical ventilation Patients with severe air leak syndromes (e.g., bronchopleural fistula) Common clinical scenarios for V-V ECMO include ARDS from various causes, status asthmaticus, or as a bridge to lung transplantation in end-stage lung disease	Refractory cardiogenic shock with or without concomitant respiratory failure Common clinical scenarios for V-A ECMO include acute myopericarditis, postcardiotomy, severe hypothermia with cardiac arrest, or refractory ventricular fibrillation (as a bridge to revascularization)
Contraindications	Absolute Moribund patients with established multiple organ failure Patients with poor short-term prognosis (e.g., metastatic malignancy) Patients with other advanced comorbidities that preclude return to meaningful function if ECMO support is weaned	Absolute Patients with nonrecoverable cardiac function who are not candidates for transplantation or long-term mechanical ventricular assist device implantation Relative Contraindications to therapeutic-dose anticoagulation
	Relative Contraindications to therapeutic-dose anticoagulation High-intensity mechanical ventilation for >7 d Advanced age Limited vascular access	Severe aortic regurgitation Aortic dissection Existent multiple organ failure Advanced age Limited vascular access

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; V-A = venoarterial; V-V = venovenous.
Some of the information in this table is included from Reference 12.

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Right Heart Failure

Peter Hountras and Michael J. Cuttica

Definition of Right Heart Failure

Classically, cardiopulmonary physiology teaching has focused on left heart function, but it is now clear that both acute and chronic right heart failure states are important drivers of morbidity and mortality (1, 2). Right heart failure is a condition whereby dysfunction of the right ventricle leads to decreased cardiac output despite a normal or elevated central venous pressure (3). A better understanding of the causes, recognition, and approaches to treatment is necessary to care for patients with this entity.

Causes of Right Heart Failure

The wide variety of problems that can cause right heart failure can be categorized according to their underlying pathophysiology (Table 6). Acute right heart failure is commonly driven by precipitators of critical illness, such as acute pulmonary embolism, right ventricular infarction, sepsis, and acute respiratory distress syndrome. Patients with underlying conditions, such as pulmonary arterial hypertension, chronic lung disease, or left-sided heart failure, are particularly prone to acute decompensation of the right ventricle related to any added stressors, such as infections or volume shifts.

Diagnostic Strategy

Diagnosing right heart failure can be difficult, especially in the acute setting where illnesses, such as sepsis, have hemodynamic effects beyond the right ventricle. Common presenting symptoms such as dyspnea and fatigue are nonspecific. Physical examination signs can be either difficult to appreciate (tricuspid murmurs or accentuated second heart sounds) or overlap with other disease states (elevated jugular venous pulsation, edema, and ascites). Current guidelines recommend a stepwise approach to systematically evaluate for conditions that cause pulmonary hypertension and right heart dysfunction (Figure 3) (4). Transthoracic echocardiography allows direct visualization of right ventricular function, allowing for measurements of right

Table 6. Causes of right heart failure

Physiologic Change	Etiology
Increased right ventricular afterload	Left heart disease (increased left heart filling pressures) Acute pulmonary embolism Pulmonary arterial hypertension Pulmonary hypertension due to lung disease Chronic thromboembolic pulmonary hypertension Acute lung injury/ARDS (hypoxic vasoconstriction) Post cardiothoracic surgery Pulmonic stenosis
Impaired right ventricular contractility	Right ventricular infarction Sepsis Cardiomyopathy
Increased right ventricular preload	Acute volume loading in the setting of underlying pulmonary vascular disease Tricuspid regurgitation Pulmonic regurgitation Post left ventricular assist device Unrepaired atrial/ventricular septal defect

Definition of abbreviation: ARDS = acute respiratory distress syndrome.
Adapted by permission from Reference 3.

heart chamber size, pulmonary artery systolic pressure, interventricular septal motion, and the tricuspid annular plane systolic excursion. An increase in right atrial/ventricular size and decrease in right ventricular function and tricuspid annular plane systolic excursion are consistent with right heart failure. More detailed hemodynamic information related to preload, afterload, and contractility can be obtained by right heart catheterization. Although routine use of right heart catheterization in patients with shock and respiratory failure is not indicated, it remains the gold standard for both diagnosis and guiding appropriate therapy in patients with clinical signs of right heart failure.

Management of Right Heart Failure

Effective management relies on identification of the underlying cause and understanding its effects on preload, afterload, and contractility of the right heart.

Preload. Optimization of right ventricular preload is essential for maintaining cardiac output while awaiting resolution of the cause of right heart failure (5). A detailed discussion of strategies to assess volume status in right heart failure is beyond the scope of this review. It is important to recognize that although some patients with right heart failure do benefit from careful fluid administration, many patients are volume overloaded and require diuresis. The dilated failing right ventricle is very sensitive to further volume loading, and it is not uncommon that patients with acute right heart failure will benefit from diuresis even in the setting of hypotension (6, 7).

Afterload. Optimization of afterload is achieved through either pulmonary vasodilation or relief of obstruction in the pulmonary vascular bed by, for example, lysis of a pulmonary embolism (8). Reversing alveolar hypoxia is an important intervention for all patients with right heart failure and is frequently a target intervention for those with right heart failure from acute illness. Correction of hypoxemia allows vasodilation of the vascular bed and decreases afterload. Inhaled pulmonary vasodilators, including nitric oxide and epoprostenol, are the agents of choice in the acute setting due to their selective pulmonary vasodilation and short half-life. In patients with pulmonary arterial hypertension, multiple drugs targeting the endothelin, nitric oxide, and prostacyclin pathways are available and well-studied in patients with chronic pulmonary vascular disease (9). The role of these drugs in other forms of right heart failure is unknown and somewhat controversial at this time.

Contractility. Optimization of cardiac contractility may require reversing right ventricular ischemia and/or the use of inotropic support (5). Because the dilated right ventricle is prone to ischemia, maintenance of adequate systemic blood pressure helps ensure adequate coronary perfusion. Reversing hypoxemia and optimizing preload to reduce right ventricular dilatation are also important for maintaining right ventricle contractility. The role of inotropic agents in right heart failure is less clear, as finding a suitable balance between beneficial improved contractility and deleterious increased oxygen demand and side effects such as systemic hypotension and tachyarrhythmia is challenging (10). Clinicians should approach the use of these drugs cautiously.

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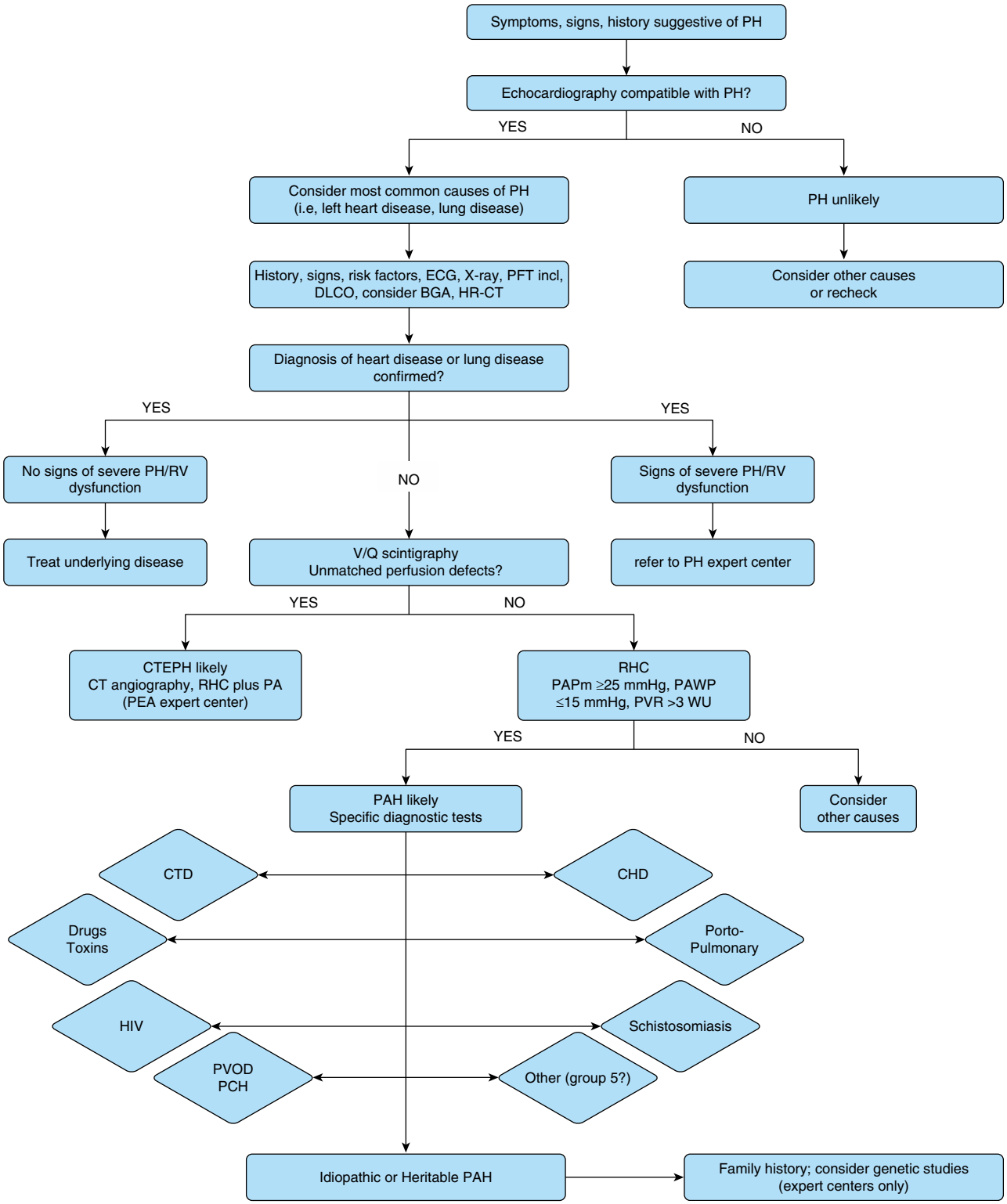

Figure 3. Diagnostic approach to pulmonary hypertension. BGA = blood gas analysis; CHD = congenital heart disease; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; HR-CT = high-resolution computed tomography; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PCH = pulmonary capillary hemangiomatosis; PEA = pulmonary endarterectomy; PFT = pulmonary function testing; PH = pulmonary hypertension; PVOD = pulmonary venoocclusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheter; RV = right ventricle; W = Wood units. Reprinted by permission from Reference 4.

Volume Responsiveness

Morgan Soffler and Kathryn A. Hibbert

Background

The primary goal of resuscitation in sepsis is to ensure adequate cardiac output and tissue oxygen delivery. Given data demonstrating an association between increased fluid administration and mortality in critically ill patients, determining when to administer fluids rather than vasopressors during resuscitative efforts is a fundamental dilemma faced by all critical care practitioners (1). Although resuscitation protocols previously emphasized the role of central venous pressure (CVP) in determining the suitability of volume administration, more recent guidelines now emphasize basing decisions on "dynamic" measures of volume responsiveness (2).

Defining the Term "Volume Responsive"

The Frank-Starling curve describes the ability of the myocardium to augment cardiac output (CO) in response to increased preload (i.e., right ventricular end-diastolic volume or right atrial pressure [RAP]) (Figure 4, *line a*). Venous return (VR) is determined by the difference between mean systemic filling pressure (MSFP) (Figure 4, *point c*), which is an equilibration pressure at zero flow (CO = 0) and RAP, and is affected by intravascular volume and vascular tone (3). The Guyton curve represents VR along a range of RAP and therefore the availability of volume to the heart (Figure 4, *line b*). The point where the VR and CO curves intersect (Figure 4, *point d*) represents the actual VR, CO, and CVP for an individual. With volume administration, the point of intersection of the VR and CO curves may move along the ascending or plateau portion of the CO curve (3). Volume responsiveness is therefore defined as an increase in CO in response to an increase in MSFP (Figure 5).

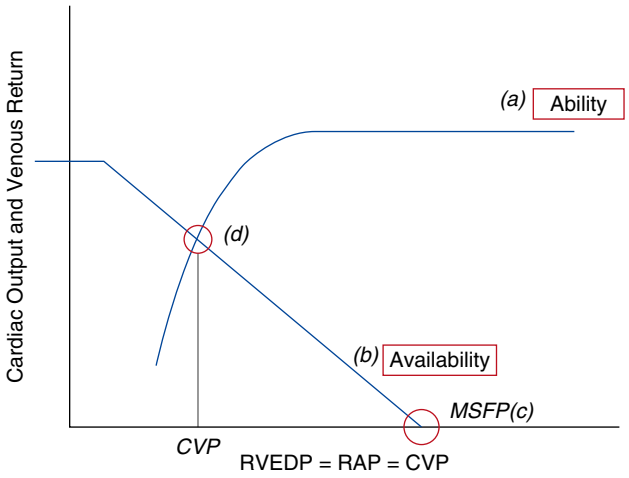

Figure 4. The Frank-Starling (*a*, ability) and Guyton analysis or venous return curves (*b*, availability). The curves demonstrate the possible cardiac output (CO) and venous return (VR) along a range of right atrial pressure (RAP). Point *c* is the mean systemic filling pressure (MSFP). Point *d* represents the actual VR, CO, and central venous pressure (CVP) for a given individual. RVEDP = right ventricular end-diastolic pressure.

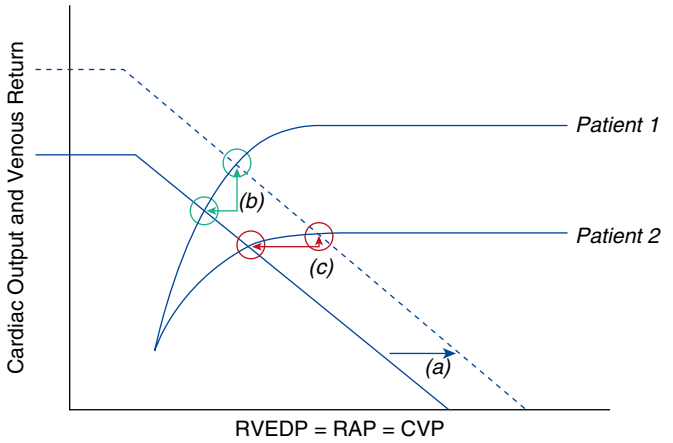

Figure 5. Volume responsiveness. With fluid administration, the mean systemic filling pressure (MSFP) is increased and venous return curve is shifted to the right (*a*). Patient 1 has an increase in cardiac output (CO) with an increase in MSFP (*b*). Patient 2 has little increase in CO with an increase in MSFP (*c*). CVP = central venous pressure; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure.

Static Measures and the Appropriate Use of CVP

CVP has traditionally been used to gauge volume status and received further emphasis after a study by Rivers and colleagues, which incorporated a target CVP of 8 to 12 cm H_2O in their early goal-directed therapy protocol (4). Multiple clinical studies, however, have demonstrated that CVP and other static measures, including pulmonary artery occlusion pressure and inferior vena cava diameter, are poor predictors of volume responsiveness (5, 6). However, observing changes in CVP after fluid administration can be valuable in assessing the adequacy of the volume challenge (7). If empiric fluid does not result in an increase in CVP of ~2 cm H_2O, then the MSFP has not increased and no conclusion can be drawn about the patient's fluid responsiveness.

Dynamic Measures of Volume Responsiveness

Dynamic measures of volume responsiveness assess changes in CO (or a proxy measure) in response to changes in VR that occur due to changes in RAP or MSFP. For example, respiratory activity changes RAP and, as a result, tests the CO response to changes in VR. During spontaneous respiration, RAP decreases and VR increases with inspiration in response to decreased intrathoracic pressure. The opposite occurs in passive patients ventilated with positive pressure. Alternatively, clinicians can manipulate the MSFP by increasing VR through either an empiric volume challenge or a passive leg raise maneuver to mobilize blood held in the capacitance veins of the lower extremities.

Several bedside strategies for manipulating MSFP and RAP have been studied and found to be good predictors of fluid responsiveness (Table 7). Before performing the maneuvers, clinicians must either measure CO directly (e.g., thermodilution, noninvasive cardiac output monitor) or designate a proxy measure (pulse pressure, pressor requirement, etc.) and then assess change in CO or the proxy with changing VR. Although the goal of this approach is to prevent fluid nonresponders from receiving fluids that are not beneficial and possibly harmful, none of these approaches is 100% sensitive for identifying volume responders, and each has strengths and limitations (8). The gold

Table 7. Dynamic maneuvers to predict volume responsiveness

Maneuver	Physiologic Effect	Strengths	Limitations
Passive leg raise test	Increase venous return via lower extremity return blood flow.	Reversible	Requires surrogate for cardiac output during maneuver Patients may not tolerate the positioning required for the test Volume may be insufficient to raise CVP Elevated intrathoracic or intraabdominal pressures may blunt increase in venous return
PPV with respiration	Increase intrathoracic pressure during mechanical ventilation → increase in RAP PPV of 13% predicts volume responsiveness.	Change in pulse pressure is a better predictor of change in cardiac output than a change in systolic pressure	Patient must be passively ventilated Need adequate changes in intrathoracic pressure (~8 ml/kg) Need normal sinus rhythm Not validated in studies on lung-protective ventilation Not validated in patients with low lung compliance
IVC collapsibility (spontaneous breathing)	Decrease in intrathoracic pressure → increase in venous return → IVC collapsibility IVC < 2 cm with >50% collapse with each breath or IVC collapse > 12% predicts volume responsiveness	No arterial or central line needed	Requires ultrasound skill Interobserver variability Elevated intrathoracic or intraabdominal pressures may blunt IVC distention
IVC distensibility (passive ventilation)	Increase in intrathoracic pressure → decrease in venous return → IVC distention IVC distensibility > 18% predicts volume responsiveness	No arterial or central line needed	Requires ultrasound skill Interobserver variability Elevated intrathoracic or intraabdominal pressures may blunt IVC distention
Fluid challenge	Increase in MSFP → increase in venous return	A smaller bolus of fluid can be administered quickly via a "mini-bolus" challenge	Requires surrogate for cardiac output Not readily reversible

Definition of abbreviations: CVP = central venous pressure; IVC = inferior vena cava; MSFP = mean systemic filling pressure; PPV = pulse pressure variation; RAP = right atrial pressure.
Some tests are used to predict fluid responsiveness, but the gold standard is a fluid challenge, the adequacy of which can be assessed by change in CVP after fluid provided.

standard test remains a volume challenge during which the CO response (or a proxy) to empiric fluid bolus is observed.

There is currently no standard approach to how much volume to administer as part of a volume challenge. Although an increase in CVP indicates adequate volume has been given to assess the response, the volume necessary to achieve that may vary between patients. Several recent small studies have attempted to mitigate the risk associated with excess fluid administration by studying a "mini-bolus" fluid challenge. One hundred milliliters of colloid administered over 1 minute and 50 ml of crystalloid infused over 10 seconds have been studied and have shown to be good predictors of volume responsiveness when compared with 500 ml of crystalloid (9, 10).

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Update in Early Goal-Directed Therapy

Timothy Leclair and Ryan Clouser

Background

Resuscitation of patients with severe sepsis and septic shock has evolved significantly in the past 15 years. After a landmark trial, increasing attention was focused on the early identification and resuscitation of patients with sepsis using a protocolized approach to care, and in recent years multiple large randomized trials have led to refinements in the recommended practice (1–4). Early diagnosis and treatment leads to improved outcomes. Maintaining perfusion is paramount to the prevention of multisystem organ failure and death. Resuscitation, targeting end points like mean arterial pressure (MAP), urine output, mental status, capillary refill, and lactate clearance, has been shown to decrease mortality for patients with severe sepsis and septic shock (1, 5).

In their seminal 2001 study, Rivers and colleagues randomized patients to usual care in the emergency department or early initiation (within 6 h of identification) of a resuscitation protocol targeting specific end points, including CVP 8 to 12 mm Hg, MAP greater than 65 mm Hg, central venous oxygen saturation greater than or equal to 70%, and urine output greater than 0.5 ml/kg/h, referred to as early goal-directed therapy (EGDT) (1). Patients in the treatment arm received fluids, vasopressors, blood transfusions, and inotropic agents on the basis of an algorithm. This bundled intervention was associated with an absolute risk reduction in mortality of 16% when compared with standard care.

Recent Evidence

Although the results of this study highlighted the importance of early recognition and treatment of sepsis and led to significant changes in practice, several important concerns were raised about the trial, including the high mortality rate in the control arm and its wider applicability outside the emergency department setting. Questions were also raised about which particular aspect of the protocol was driving the observed benefit and whether, for example, red blood cell transfusion, which has been associated with multiple adverse outcomes in other studies, was necessary within the protocol.

These questions prompted three large, multicenter randomized controlled trials to further clarify the best approach to sepsis care (2–4). These studies randomized patients with sepsis to receive a less stringent resuscitation protocol or standard care against the early goal-directed protocol that mandated a central venous catheter and often prompted red cell transfusion. The major outcomes are displayed in Table 8. In ProCESS (Protocolized Care for Early Septic Shock), there was no difference in mortality between the EGDT group and the usual care group, who was managed without a required transfusion goal, mandated central line placement, or CVP monitoring (2). These results were similar to the ARISE (Australasian Resuscitation in Sepsis Evaluation) trial, where the usual care group did not undergo central venous oxygen saturation monitoring (3). Similarly, the most recent trial, ProMISe (Protocolized Management in Sepsis), also showed no difference in mortality between the EGDT group, who received continuous central venous oxygen monitoring and a 6-hour resuscitation protocol, and the control group, who received usual care decided on by the physicians treating those patients (4). A planned systematic review and meta-analysis of the data from these three trials showed no evidence of improved survival for patients receiving EGDT versus standard care (6).

Table 8. Results of early goal-directed therapy trials

	Rivers*		ProCESS†			ProMISe†		ARISE†	
	Control	EGDT	Modified EGDT	PBSC	Usual Care	Modified EGDT	Usual Care	Modified EGDT	Usual Care
N	133	130	439	446	456	630	630	796	804
Fluid volume, 72 h, ml	13,358‡	13,443‡	7,253‡	8,193‡	6,633‡	3,623§	3,981§	4,274‡	4,382‡
Central line,‖ %			93.6	56.5	57.9	92.1	50.9	13.7	61.9
VP, %	51.3	36.8	60.4	61.2	53.7	57.9	52.6	58.8	51.5
Dobutamine, %	9.2	15.4	9.3	2.5	2.9	17.7	6.5	9.5	5.0
Blood transfusion, %	44.5	68.4	27.3	24.0	22.4	12.6	8.5	11.0	11.8
APACHE II	20.4	21.4	20.8	20.6	20.7	18.7	18.0	15.4	15.8
ICU admit, %			91.3	85.4	86.2	88.2	74.6		
Central venous O_2, %	65.3	70.4						75.9	NA
Mortality, %	46.5¶	30.5¶	21.0**	18.2**	18.9**	29.5††	29.2††	18.6††	18.8††

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARISE = Australasian Resuscitation in Sepsis Evaluation; EGDT = early goal-directed therapy; ICU = intensive care unit; NA = not applicable; PBSC = protocol-based standard care; ProCESS = Protocolized Care for Early Septic Shock; ProMISe = Protocolized Management in Sepsis; VP = vasopressor.
*Single-center trial (1).
†Multicenter trial.
‡Mean.
§Median.
‖Within 6 h.
¶In-hospital mortality.
**In-hospital death by 60 d.
††90-d mortality.

On the surface, these studies raise important questions about the utility of the heavily protocolized EGDT approach. However, with the increased emphasis on early recognition and resuscitation after the trial by Rivers and colleagues (1), the standard of care has evolved such that it contains many elements of the EGDT approach and, as a result, is likely very different than the standard of care at the time of the original EGDT trial.

Current Guidelines

With that caveat in mind, these recent studies and the meta-analysis that followed indicate that the approach to sepsis resuscitation can be simplified. Clinicians should emphasize early administration of broad-spectrum antibiotics, preservation of MAP greater than or equal to 65 mm Hg, and early fluid resuscitation. The current Society of Critical Care Medicine surviving sepsis guidelines recommend administration of 30 ml/kg of crystalloid within the first 3 hours of presentation. Rather than CVP, fluid administration should be guided by dynamic measures of volume responsiveness where available. Blood transfusions should be avoided as a means of optimizing oxygen delivery except with active hemorrhage, myocardial ischemia, or severe anemia (hemoglobin < 7 g/dl). Routine central venous oxygen saturation monitoring is unnecessary, and dobutamine should be considered when there is evidence of persistent hypoperfusion despite adequate fluid loading and vasopressor agents (7). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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